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EXAMINER

SPECTOR, L

ART UNIT

1647

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Part III: Detailed Office Action

Restriction Requirement:

Applicant's election with traverse of Invention I, with a further election of species 12D5 in Paper No. 12 submitted 11/24/99 is acknowledged. The traversal is on the ground(s) that (1)the groups of inventions are not independent, and (2) the examination of the entire application would not constitute a burden to search. This is not found persuasive because with respect to point (1) above, the inventions are distinct as noted in the last Office Action, as shown by the distinctness described therein. Applicant's attention is directed to MPEP 806.05. With respect to point (2) above, contrary to applicants' assertion that any search of the prior art in regard to group I will reveal whether any prior art exists as to the other Groups, a search is directed to references which would render the invention obvious, as well as references directed to anticipation of the invention, and therefore requires a search of relevant literature in many different areas of subject matter. Further, applicants argument appears to be directed more to unity of invention than to restriction practice under 35 U.S.C. §121. For example, with respect to Invention IV, drawn to nucleic acids encoding the claimed antibodies, it is well established in U.S. patent law that possession of a protein does not necessarily make the nucleic acid encoding that protein obvious, and further, the nucleic acid and protein are physically and functionally distinct molecules which require separate searches.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-5, 7-9 and 11-19 are under consideration. Claims 6, 10 and 20-42 are withdrawn from consideration as being drawn to non-elected species or inventions.

Formal Matters:

The use numerous trademarks such as SEPHAROSE, MONO-SEQ ID NO:, etc. (see page 23) has been noted in this application. Trademarks should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature

of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim 9 is objected to for encompassing non-elected species. Correction is required.

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Objections and Rejections under 35 U.S.C. §112:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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Claims 1-5, 7-9 and 11-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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Claim 1 is indefinite as it is not clear what receptor *other* than c-mpl the claim may encompass. The recitation of “a thrombopoietin receptor” would seem to indicate that the claim is intended to be broader than that to an agonist of c-mpl, and it is not clear what else is intended to be encompassed.

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Claim 1 is further indefinite as it is not clear whether only the antibody is required to have the activity of binding to a thrombopoietin receptor, or whether the fragment or variant must also have that function. In the interest of compact prosecution, the Examiner will apply the prior art as though the fragment or variant were required to retain tpo receptor binding function.

Claim 11 is indefinite because one of the primary functions of c-mpl receptor is to, when stimulated by an agonist, stimulate megakaryocytes to produce platelets. Thus, it is not clear how an agonist antibody could be defined as *not* having that function.

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Claim 15 is indefinite for failing to further limit the claim from which it depends. Claim 2, from which claim 15 depends, is specifically to an antibody, and not a fragment.

The remaining claims are rejected for depending from an indefinite claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

5 The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10 Claim 9 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

15 The enablement of claim(s) 9 requires availability of the specific antibodies claimed therein. This determination has been made because said antibodies are not fully disclosed nor have they been shown to be publicly known and freely available. Accordingly, it is deemed that a deposit of plasmids containing sequences encoding these antibodies or hybridomas which produced the antibodies should have been made in accordance with MPEP Chapter 2400 and 37 C.F.R. §§1.801-1.809. Applicant is advised that the Patent Office accepts Budapest approved deposits, as long as assurance is provided that the deposited material will be made irrevocably available with no restrictions upon issuance of a patent. See MPEP Chapter 2400. While this has been done, the statement of deposit at page 57 of
20 the specification is not in compliance with 37 C.F.R. § 1.806, which states:

25 A deposit made before or during pendency of an application for patent shall be made for a term of at least thirty (30) years and at least five (5) years after the most recent request for the furnishing of a sample of the deposit was received by the depository. In any case, samples must be stored under agreements that would make them available beyond the enforceable life of the patent for which the deposit was made.

30 While the deposit statement at page 57 states that the deposit will be for a term of at least 30 years, it omits to state that the deposit will be maintained for at least five (5) years after the most recent request for the furnishing of a sample of the deposit was received by the depository.

 Claims 1-3, 5, 7, 8 and 11-19 are rejected under 35 U.S.C. 112, first paragraph, as

containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is not commensurate in scope with claims to agonist antibodies to any receptor other than one identified as MPL or c-MPL (claim 1). Enablement is also not commensurate in scope with an agonist antibody to a thrombopoietin receptor which agonist antibody does *not* stimulate megakaryocytes to produce platelets (claim 11).

As stated in the rejection under 35 U.S.C. §112, second paragraph, above, claim 1 appears to encompass agonist antibodies to receptors other than MPL. The specification discloses only mpl as being the thrombopoietin receptor, and discloses no other TPO receptors. It would require undue experimentation to make or find other TPO receptors and then to make agonist antibodies to said receptors. The specification provides no guidance or direction for such, and while it is believable that such could be found or made, without guidance, direction or any working example of such, and in view of the prior art, which does not recognize any TPO receptor other than MPL, it would require undue experimentation to practice the invention in a manner commensurate in scope with the claims.

With regard to enablement of an agonist antibody to a thrombopoietin receptor which agonist antibody does *not* stimulate megakaryocytes to produce platelets, while thrombopoietic activity is definite at page 13 of the specification as being “biological activity that consists of accelerating the proliferation, differentiation and/or maturation of megakaryocytes of megakaryocyte precursors into the platelet producing form of these cells”, which would include the stimulation of megakaryocytes to produce platelets, there has been no ‘dissection’ or separation of those functions. That is, there is no teaching in the specification or in the prior art as a whole, that the receptor itself can be differently stimulated to produce one or more, but not all of the aforementioned functions. If it is possible to effect one of those functions specifically, without inducing the others, such is more likely to be due to the presence of costimulatory cytokines, or the nature of the cell being stimulated, than it is to be due to a difference in how the receptor is bound. Accordingly, it is not predictable that an agonist antibody could be made which would *not* stimulate megakaryocytes to produce platelets,

given the right conditions. In view of the absence of any guidance in the specification, the absolute lack of any working example of such, and the absence of recognition in the art that such an agonist could be made, it is found that it would require undue experimentation to make and the specification is not enabling of, an agonist antibody to a thrombopoietin receptor which agonist antibody does *not* stimulate megakaryocytes to produce platelets.

Rejections Over Prior Art:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-5, 8, and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by B. Deng et al., Experimental Hematology 24:1072, 1996. Deng et al. disclose monoclonal antibody BAH-1, which is agonistic for human C-MPL. Although Deng et al. is silent with respect to the production of platelets (claim 4), this feature is presumed to be inherent to an agonistic antibody to C-MPL; see discussion above under 35 U.S.C. §112, first paragraph (scope) rejection.

Claims 1-5, 7, 8, 13, 15 and 17 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent Number 5,980,893 (Avraham et al.). Avraham et al. disclose agonist murine monoclonal antibodies to human C-MPL, and therapeutic compositions comprising such; see abstract, paragraph

bridging columns 1-2. Chimeric and human antibodies are disclosed at column 4 line 56. Active fragments of the antibodies are disclosed at column 5, lines 30+. It is noted that monoclonal antibodies are non-naturally occurring. Pharmaceutical compositions are discussed at column 2 line 37+ and column 5 lines 48-54. Although the patent is silent with respect to the production of platelets (claim 4), this feature is presumed to be inherent to an agonistic antibody to C-MPL; see discussion above under 35 U.S.C. §112, first paragraph (scope) rejection.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent Number 5,980,893 (Avraham et al.). The teachings of Avraham et al. are discussed above. Although Avraham et al. disclose pharmaceutical compositions comprising C-MPL agonistic antibodies, they do not specifically state that those compositions should be sterile nor lyophilized.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to lyophilize the pharmaceutical composition of Avraham et al., as the person of ordinary skill in the art would have known that lyophilization is a process commonly used to store biologically active proteins in stable form, and would have desired the known and expected advantages of being able to store the pharmaceutical composition in a stable form. It would also have been obvious to

the person of ordinary skill in the art at the time the invention was made to make the pharmaceutical composition of Avraham et al. sterile, as the person of ordinary skill in the art at the time the invention was made would have known that it is almost always desirable to have a pharmaceutical composition in sterile form, both to avoid contamination, and to increase shelf life.

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Claims 12 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent Number 5,980,893 (Avraham et al.) or Deng et al., either one in view of U.S. Patent Number 5,635,388 (Bennett et al). The teachings of Avraham et al. and Deng et al. are discussed above. Avraham et al. and Deng et al. do not specifically disclose labeling the antibody (claim 12) nor immobilization of the antibody on an insoluble matrix.

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Bennett et al. disclose agonist antibodies to another hematopoietic cytokine receptor, the Flk2/Flt3 receptor. At column.12, beginning at line 62, Bennett et al. disclose labeling the agonistic antibodies for diagnostic use. At column 13, lines 30-32, Bennett et al. disclose immobilization of the antibodies on a solid support for the purpose of performing sandwich immunoassays, a procedure for the detection of the receptor to which the antibodies bind. At col. 15, lines 63-67, Bennett et al. state that the antibodies “ are useful in diagnostic assays for flt2/flk3, e.g., detecting its expression in specific cells, tissues, or serum. The antibodies are labeled flk2/flt3 and/or are immobilized on an insoluble matrix.”

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It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the antibodies of Avraham et al. or Deng et al. by labeling them or attaching them to an insoluble matrix, as taught by Bennett et al. One of ordinary skill in the art would have been motivated to do so to perform diagnostic assays as taught by Bennett et al., and would particularly have been motivated to apply Bennett’s teachings to the MPL receptor agonist antibodies of Avraham et al. or Deng et al. because of the common functions of the receptors involved, and would have expected success at performing the modifications, as both labeling and immobilization of antibodies are old and well known in the art. Accordingly, the invention as a whole was *prima facie* obvious at the time the invention was made.

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5 Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent Number 5,980,893 (Avraham et al.) or Deng et al., either one in view of U.S. Patent Number 4,946,778 (Ladner et al). The teachings of Avraham et al. and Deng et al. are discussed above. Although Avraham et al. and Deng et al. disclose C-MPL agonistic antibodies, they do not specifically disclose single chain antibodies.

 Ladner et al. teach the construction of single chain antibodies . The stated advantages of such as enumerated at column 3 lines 32-48 include smaller size, greater stability, lower cost, lower immunogenicity, etc.

10 It would have been obvious to the person of ordinary skill in the art at the time the invention was made to substitute the C-MPL agonistic antibodies of Avraham et al. or Deng et al. into the single chain or humanized antibodies of Ladner et al. to attain the known and expected advantages of such as set forth by Ladner et al. and as referred to above. Ladner clearly teaches both the desirability of such single chain antibodies, as well as the general applicability of the disclosure.

15 **Advisory Information:**

 Claims 9 and 11 are free of the prior art. No claim is allowed.

Serial Number 09/138091
Art Unit 1646

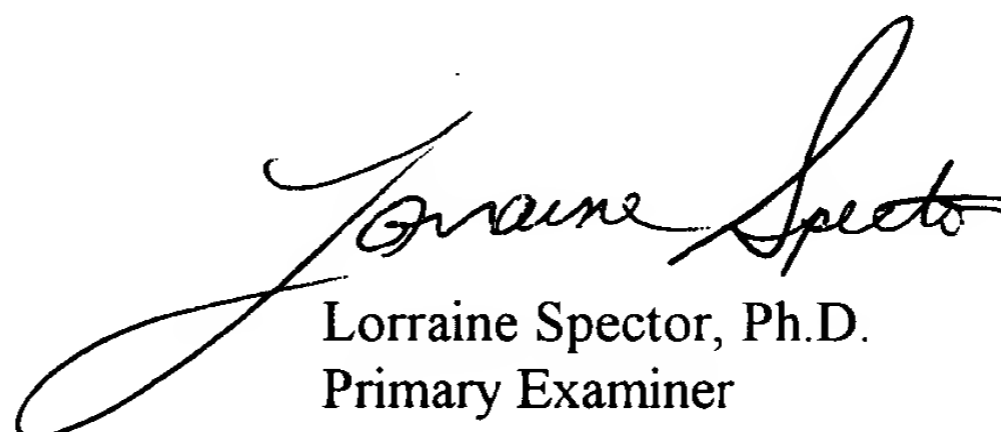
Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector, whose telephone number is (703) 308-1793. Dr. Spector can normally be reached Monday through Friday, 8:00 A.M. to 4:30 P.M.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached at (703)308-4623.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist at telephone number (703) 308-0196.

Certain papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to (703) 305-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. **Please** advise the Examiner at the telephone number above when an informal fax is being transmitted.



Lorraine Spector, Ph.D.
Primary Examiner

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